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BULLETIN OF
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A THEORY OF MEMBRANE PERMEABILITY: I

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As a first approximation, a membrane is considered as a potential barrier or potential well for the molecules which diffuse through it. Making some simple assumptions about the form of that potential barrier or well, the author sets up and integrates the differential equation for the diffusion of the molecules through the membrane under the influence of the potential field.

A plane membrane may be conveniently thought of as a collection of molecules, hereinafter known as "membrane molecules", located between two parallel planes. Associated with this membrane and any given substance diffusing through it is a potential function, whose value at any point can be taken to be the amount by which the potential energy of a molecule of the diffusing substance (the "solute") at that point exceeds its potential energy an infinite distance away from the membrane. This function may be predominantly either negative or positive in the membrane, according as the membrane is a potential "well" or "barrier".

The normal to the membrane will be defined as the x-axis; the flat region occupied by the membrane extends from $x = -b$ to $x = +b$. Symbols to be used are defined below:

$J =$ grams/cm.^{2} sec. of solute passing through the membrane in the $+ x$ direction (J is constant in x).

$D(x) =$ diffusion coefficient.

$c(x) =$ concentration of the solute, in gm./cc. $\begin{cases} c_0 = c(-B_1). \\ c_1 = c(B_2). \end{cases}$

$$c' \equiv \frac{dc}{dx}.$$

$V(x) =$ potential function. $V(x) = 0$ if $x > B_2$ or $x < -B_1$.

$$V' \equiv \frac{dV}{dx}.$$

$T(x) =$ temperature. $T(B_2) = T(-B_1) = T_0$.

$k =$ Boltzmann's constant $= 1.371 \times 10^{-16} \dfrac{\text{ergs}}{\text{deg.C}}$.

$h =$ membrane permeability.

$\lambda =$ mean free path of solute molecules.

$\overline{v}(x) =$ average velocity of solute molecules.

$\overline{v^2}(x) =$ mean square velocity of solute molecules.

$n_w(x) =$ number of molecules of solvent (water) per cc.

$n_m(x) =$ number of membrane molecules per cc.

$$\begin{aligned} n_m(x) &= 0 \text{ for } -\infty < x < -b, \\ &\qquad \text{and } b < x < \infty. \\ n_m(x) &= N \qquad \text{for } -b \leqq x \leqq b. \end{aligned}$$

$r_w =$ radius of water molecule (assumed spherical).

$r_m =$ radius of membrane molecule (assumed spherical).

$r_s =$ radius of solute molecule (assumed spherical).

$R_1 \equiv r_s + r_w$.

$R_2 \equiv r_s + r_m$.

$m =$ mass of solute molecule.

$\alpha =$ volume per cc. occupied by neither water nor membrane molecules.

Equation (1) below describes the motion of a diffusing substance in a force field.

$$c' + \frac{cV'}{kT} + \frac{J}{D} = 0. \tag{1}$$

The solution of this equation can be written

$$c = e^{-\int [V'(x)/kT(x)]dx} \left[a - J \int_{-B_1}^{x} \frac{e^{\int [V'(x)/kT(x)]dx}}{D(x)} dx \right] \tag{2}$$

where a is a constant of integration.

The temperature is proportional to average molecular kinetic energy, and may, therefore, be approximately written as

$$T(x) = T_0 - \frac{2}{3k} V(x), \tag{3}$$

if

$$V(x) < \frac{3}{2} kT_0 .$$

A more accurate expression for T might be

$$T(x) = T_0 - \frac{2}{3k} V(x + \Delta x) , \tag{4}$$

where Δx is inserted because in a liquid the average kinetic energy of molecules at x may be influenced by collisions with clumps of molecules whose centers of gravity are at positions denoted by other values of x. The quantity Δx is positive or negative according as J is negative or positive.

Such is the approximate nature of this treatment that equation (3) will be taken as giving T:

$$\int \frac{V'(x)\,dx}{kT(x)} = \frac{1}{k} \int \frac{dV}{T_0 - \frac{2}{3k} V} = -\frac{3}{2} \log \left(T_0 - \frac{2}{3k} V \right) . \tag{5}$$

Equations (2) and (5) yield

$$c = \left(T_0 - \frac{2}{3k} V(x) \right)^{3/2} \left[a - J \int_{-B_1}^{x} \frac{\left(T_0 - \frac{2}{3k} V(x) \right)^{-3/2}}{D(x)} dx \right] ; \tag{6}$$

since $c_0 = c(-B_1)$ and $V(-B_1) = 0$,

$$a = \frac{c_0}{T_0^{3/2}} . \tag{7}$$

Further,

$$c_1 = c_0 - J\, T_0^{3/2} \int_{-B_1}^{B_2} \frac{\left[T_0 - \frac{2}{3k} V(x) \right]^{3/2} dx}{D(x)} . \tag{8}$$

The permeability h is defined by

$$h(c_0 - c_1) = J ; \tag{9}$$

hence,

$$h = \frac{T_0^{-3/2}}{\displaystyle\int_{-B_1}^{B_2} \frac{\left[T_0 - \frac{2}{3k} V(x) \right]^{-3/2}}{D(x)} \, dx} . \tag{10}$$

An approximate expression for D is

$$D = \frac{1}{3} \bar{v} \lambda ; \tag{11}$$

λ can be approximated as

$$\lambda = \frac{1}{\pi (n_w R_1^2 + n_m R_2^2)} . \tag{12}$$

If the solute is greatly diluted, n_w may be considered to be influenced only by virtue of the membrane molecules' occupying space which would otherwise be occupied by water molecules, or the sum of the volumes/cc. occupied by the two types of molecules may be set constant:

$$\frac{4}{3} \pi (r_m^3 n_m + r_w^3 n_w) = 1 - \alpha ; \tag{13}$$

this gives

$$n_w = \frac{3}{4\pi} \frac{(1 - \alpha)}{r_w^3} - \frac{r_m^3 n_m}{r_w^3} . \tag{14}$$

Equation (14) will subsequently be used for substitution in equation (12).

It is approximately true that

$$\bar{v} = \sqrt{\overline{v^2}} ; \tag{15}$$

strict accuracy would require the use of a multiplicative constant of value (determined by the type of molecular velocity distribution) about equal to unity. If E_0 is the average translational kinetic energy of a solute molecule at $x = B_2$ or $-B_1$,

$$\frac{1}{2} m \overline{v^2} \cong \frac{1}{2} m \bar{v}^2 = E_0 - V = \frac{3}{2} k T_0 - V , \tag{16}$$

or

$$\bar{v} = \sqrt{\frac{3kT_0 - 2V}{m}} . \tag{17}$$

Substitution in equation (11) from equations (12), (14), and (17) yields

$$D = \frac{\sqrt{3kT_0 - 2V}}{3\pi\sqrt{m}\left[n_m\left(R_2^2 - \frac{R_1^2\, r_m^3}{r_w^3}\right) + \frac{3R_1^2}{4\pi}\,\frac{1-\alpha}{r_w^3}\right]}, \tag{18}$$

whence,

$$\frac{\left(T_0 - \frac{2}{3k}V\right)^{-3/2}}{D} = \frac{(3k)^{3/2}\, 3\pi\sqrt{m}}{4}\left(\frac{3}{2}kT_0 - V\right)^{-2} \left[n_m\left(R_2^2 - \frac{R_1^2\, r_m^3}{r_w^3}\right) + \frac{3R_1^2}{4\pi}\,\frac{1-\alpha}{r_w^3}\right]. \tag{19}$$

Equation (19) can be abbreviated as

$$\frac{\left(T_0 - \frac{2}{3k}V\right)^{-3/2}}{D} = a_1 (a_2 - V)^{-2}\,(a_3 n_m + a_4)\,, \tag{20}$$

where

$$a_1 \equiv \frac{3\pi\sqrt{m}\,(3k)^{3/2}}{4}, \tag{21}$$

$$a_2 \equiv \frac{3}{2}kT_0, \tag{22}$$

$$a_3 \equiv R_2^2 - \frac{R_1^2\, r_m^3}{r_w^3}, \tag{23}$$

and

$$a_4 \equiv \frac{3R_1^2}{4\pi}\,\frac{1-\alpha}{r_w^3}. \tag{24}$$

Equations (10) and (20) may now be combined:

$$h = \frac{T_0^{-3/2}}{a_1 \int_{-B_1}^{B_2} (a_2 - V(x))^{-2}\,(a_3 n_m(x) + a_4)\,dx}, \tag{25}$$

or, since $n_m = N$ or 0 according as x is between $-b$ and $+b$ or not,

$$h = T^{-3/2}/a_1\{a_4[\int_{B_1}^{-b} [a_2 - V(x)]^{-2}\, dx + \int_b^{B_2} [a_2 - V(x)]^{-2}\, dx] + (a_3N + a_4) \int_{-b}^{b} [a_2 - V(x)]^{-2}\, dx\}. \tag{26}$$

It can be seen that the quantities B_1 and B_2 determine the "spread" of $V(x)$, or the gradualness with which $V(x)$ goes to zero outside the membrane. If the force field is symmetric, $B_1 = B_2$; if $V(x) = 0$ for all $|x|$ appreciable greater than b, then $B_1 = B_2 = b$, and the first two integrals in equation (26) vanish. If the potential energy of a solute molecule at distance r from a membrane molecule is given by A/r^s, then $V(x)$ will be roughly $\dfrac{A'}{(x-b)^{s-2}}$ for $x > b + \delta$, and $\dfrac{A'}{(x+b)^{s-2}}$ for $x < -b - \delta$, where δ is a small positive number, and A and A' are constants of the same sign (either positive or negative). The larger the quantity s, the smaller the distance $B_1 = B_2$ beyond which $V(x) \cong 0$.

The reader may be dissatisfied with the definition given for h, since its magnitude is decreased on account of the first two integrals in equation (26), which represent the resistance offered by water which is really not part of the membrane at all. However, the values of these integrals depend on a property of the membrane; namely, the potential function; furthermore, any measurement of membrane permeability will perforce include in the permeability the diffusion coefficient of a certain amount of liquid on either side of the membrane.[1] For application of equation (26) to experimental results, it is recommended that B_1 and B_2 be taken as the distances from the membrane at which c_0 and c_1, respectively, are measured.

Methods of determining $V(x)$ will be discussed in a later paper.

In conclusion, it seems advisable to evaluate h for a membrane whose potential function is constant inside the membrane, zero outside:

$$\begin{aligned} &V(x) = V_0 \text{ for } -b \leqq x \leqq b \text{, and} \\ &V(x) = 0 \text{ for } -\infty < x < -b \text{ and for } b < x < \infty. \end{aligned} \tag{27}$$

---

[1] It is of interest to note from the definitions of a_1, a_2, and a_4, that if B_1 and B_2 are chosen beyond the points where $V(x) \to 0$, the first two integrals in equation (26) will, where $V = 0$, be quite independent of the properties of the membrane, and may be seen to give the effect of resistance of the solvent alone.

In this case, $B_1 = B_2 = b$, and

$$h = \frac{T_0^{-3/2}}{a_1(a_3N + a_4) \cdot 2b(a_2 - V_0)^{-2}}, \tag{28}$$

or

$$h = \frac{2(3k)^{-3/2}\left(\frac{3}{2}kT_0 - V_0\right)^2 T_0^{-3/2}}{3\pi b\sqrt{m}\left[R_2^2 - \frac{R_1^2 r_m^3}{r_w^3}N + \frac{3R_1^2}{4\pi}\frac{(1-\alpha)}{r_w^3}\right]}. \tag{29}$$

As might be expected, h is an increasing function of α, and a decreasing function of m, b, and V_0. Equation (29) must be interpreted in light of the fact that

$$\frac{3}{2}kT_0 > V_0; \tag{30}$$

this is the condition for validity of equation (3), and must hold if equation (3) is not to indicate that negative temperatures exist within the membrane. According to the present simplified theory, a potential barrier of height $V_0 > \frac{3}{2}kT_0$ would be completely impermeable; potential wells are, *ceteris paribus*, more permeable than potential barriers.

From equation (29),

$$\frac{\partial h}{\partial T_0} \propto 3kT_0^{-3/2}\left(\frac{3}{2}kT_0 - V_0\right) - \frac{3}{2}\left(\frac{3}{2}kT_0 - V_0\right)^2 T_0^{-5/2}. \tag{31}$$

This expression has the same sign as

$$2kT_0 - \frac{3}{2}kT_0 + V_0 = \tfrac{1}{2}kT_0 + V_0, \tag{32}$$

which is positive unless

$$-V_0 \geqq \tfrac{1}{2}kT_0; \tag{33}$$

that is, permeability is an increasing function of temperature unless the membrane is a potential well of "depth" as great as that indicated by expression (33). If inequality (33) is satisfied for some temperatures, the membrane has minimum permeability when

$$-V_0 = \tfrac{1}{2}kT_0\,, \tag{34}$$

since

$$\frac{\partial h}{\partial T_0} > 0 \text{ for } T_0 > -\frac{2V_0}{k}, \tag{35}$$

and

$$\frac{\partial h}{\partial T_0} < 0 \text{ for } T_0 < -\frac{2V_0}{k}. \tag{36}$$

Dependence of h on N, the density of membrane molecules, may be seen from the following considerations: let $r_w = \beta\, r_m$. Now,

$$R_2{}^2 - \frac{R_1{}^2 \cdot r_m{}^3}{r_w{}^3} \equiv (r_s + r_m)^2 - \frac{(r_s + \beta\, r_m)^2\, r_m{}^3}{3r_m{}^3}; \tag{37}$$

this quantity is positive if

$$\beta^3 (r_s + r_m)^2 - (r_s + \beta\, r_m)^2 > 0\,, \tag{38}$$

or if

$$(\beta^{3/2} - 1)\, r_s > -(\beta^{3/2} - \beta)\, r_m\,. \tag{39}$$

Inequality (39) is valid if and only if $\beta > 1$, or h is a decreasing function of N if and only if $r_m < r_w$.

The permeability may be seen to be always positive, since

$$\frac{4\,\pi\, r_m{}^3}{3} N < 1 - \alpha, \tag{40}$$

by the definition of α.

The special case of a gas diffusing in the absence of a solvent may be treated: if there are no water molecules, expression (40) becomes an equality, and

$$h = \frac{2\,(3k)^{-3/2} \left(\frac{3}{2} kT_0 - V_0\right)^2 T_0{}^{-3/2}}{3\pi \sqrt{m}\, b\, R_2{}^2\, N}. \tag{41}$$

Equation (29) indicates that h is a decreasing function of membrane thickness and of the mass of a diffusing molecule.

The quantity $1 - \alpha$ is the same as the Van der Waalsian b; it is a measure of the closeness with which the water and membrane molecules are packed together. Therefore, h is seen to decrease with increasing closeness of packing.

The theory herein presented is, though both inaccurate and incomplete, perhaps applicable to some cases of diffusion in biological systems. The author hopes to remove some of its deficiences in later papers.

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OUTLINE OF A MATHEMATICAL THEORY OF THE REMOVAL OF MALARIAL PARASITES FROM THE BLOOD STREAM

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By making some plausible assumptions, a set of differential equations is proposed which describes the kinetics of interaction between periodically multiplying parasites and continuously produced phagocytes. These equations establish some general conditions which are necessary in order that the number of parasites should increase or decrease. Some consequences of the equations are discussed, and some experimental procedures for the determination of the parameters entering those equations are suggested.

There are certain types of diseases, of which perhaps malaria is a typical representative, which are due to infection by parasites, those parasites multiplying at rather regular intervals. This regularity of their multiplication impresses a "periodic" character on the whole course of the disease. The purpose of this paper is to outline an approach to a mathematical theory of the kinetics of interaction between the parasites and the host in this type of disease. While the following outline in its present form takes care only of the simplest aspects of the phenomena, yet, as will be seen, even in this simple form it suggests some new approaches in the experimental study. Further elaboration of the theory is likely to bring clearer insight into the observed phenomena, and to indicate new ways of experimentation in this field.

In malaria, each asexual parasite which lives in a red blood cell divides at almost regular intervals τ, called the cycle time, into a number M of new parasites. M is known as the merozoite number. Upon segmentation of the mature parasite, each new parasite enters a new erythrocyte, at least at not too late stages of the disease. Confining ourselves for the present to stages which are not too advanced, we may put the total number N of parasites equal to the number of infected erythrocytes. Moreover, the all important feature of the phenomena observed is that *all* parasites of a brood divide *almost* synchronously. Therefore, as a rather good first approximation, we may consider that the total number N of parasites in the organism increases suddenly at regular intervals of duration τ. During each of such discontinuous increases, the total number N suddenly increases M times.

Actually, however, the synchronism of division of the parasites is not perfect. There is a certain scattering around the end points of the intervals τ. Inasmuch as the rate of multiplication $p(t)$ per parasite is for all practical purposes a periodic function of period τ, it may be represented by a Fourier series:

$$p(t)=\sum_{0}^{\infty}\left(a_i \sin\frac{2\pi i t}{\tau}+b_i \cos\frac{2\pi i t}{\tau}\right). \tag{1}$$

The function $p(t)$ is practically zero everywhere, except near the end points of the intervals τ. We shall subsequently discuss how the coefficients a_i and b_i may be determined from observations.

In the absence of any other phenomena affecting the number N, such as phagocytosis or any other form of destruction of parasites, $p(t)$ represents by definition the quantity

$$(1/N)(dN/dt)=d(\log N)/dt.$$

Since after a lapse of time τ the number N increases M times, therefore for any value of t we have

$$\int_{t}^{t+\tau} p(t)\,dt=\log M. \tag{2}$$

Due to phagocytosis, the number N of parasites in the intervals between the periods of almost synchronous division does not remain constant, but decreases. Since phagocytosis of parasitized red cells occurs only in special tissues, which in the mammal are located in the spleen, the liver, and the bone marrow, the rate of removal of the total number N of parasites in the blood may be assumed to be proportional to the fraction f of the total circulation time which the blood takes to go through the phagocytic tissues. If t_p denotes the time it takes the blood to flow through the phagocytic tissues, and T is the total circulation time, then

$$f=t_p/T. \tag{3}$$

This simple definition can, however, be used only if we consider the whole circulatory system as a simple single circuit, with all parts connected in series. Actually, the circulatory system consists of a number of parallel circuits, each having a different circulation time T_i. This requires certain modification of the definition (3) as well as of the following deductions. In a subsequent paper it will be shown that those modifications do not alter fundamentally the main results.

At present we shall for simplicity consider the circulatory system as a simple circuit.

The rate of removal of the total number N of parasites will furthermore be proportional to the total number n of phagocytes present in all the phagocytic tissues. It will also be proportional to N itself. Denoting by α a coefficient of proportionality, we may set the rate of decrease of N as equal to $-\alpha fnN$. The coefficient α is essentially the probability of the removal of a particular parasitized erythrocyte during a unit of time by a particular phagocyte, when the erythrocyte is in the phagocytic tissue.

We may now write for the total rate of change of N:

$$\frac{dN}{dt} = p(t)N - \alpha fnN. \tag{4}$$

The three quantities α , f , and n are, however, not absolute constants, but in general depend themselves on the number N . As a result of their metabolic activity, the parasites produce various substances which in general may affect the above three quantities. We shall first discuss the dependence of n upon N .

In a healthy non-infected organism the number n of phagocytes is likely to be determined by the resultant of two reactions; a production of phagocytes by the tissue at a rate Q , and their natural "death rate" or destruction rate which is proportional to their number. Assuming for simplicity that Q is constant, we have, denoting by b a coefficient of proportionality,

$$\frac{dn}{dt} = Q - bn. \tag{5}$$

The number n tends asymptotically to an equilibrium value

$$n_0 = Q/b\,. \tag{6}$$

This value n_0 may be assumed to be maintained in a non-infected organism.

The metabolites produced by the parasites may, however, in general affect both the rate of production and the rate of destruction of the phagocytes. Although very little is known of the latter effect, it is definitely known that the presence of parasites stimulates the production of phagocytes. (Taliaferro and Mulligan, 1937). We shall therefore consider in this paper only this stimulating effect. In a further refinement of the theory, it may be interesting to consider an increase in the rate of destruction of n proportional to the rate of destruction of N .

The stimulating effect of N upon the rate of production of n will be represented by a function $\theta(N)$. In general, the effect of N upon dn/dt at the time t will be determined not by the instantaneous value of N, but by the value which N had at some previous time $t - t_1$. For the metabolites produced by the parasites may affect not the last stages of formation of a phagocyte, but some earlier stages.

Denoting by A a constant, we may now write

$$\frac{dn}{dt} = Q + A\,\theta[N(t - t_1)] - bn. \tag{7}$$

If α and f were constant, then the system of equations (4) and (7) would completely determine N and n at any time, if initial conditions were prescribed.

The quantity f however, is, itself likely to be affected by N. The metabolites produced by the parasites affect first of all the general circulation time due to their effect on the cardiac output. Such an effect would change t_p and T in equation (3) in the same ratio, and thus leave f unchanged. However, the metabolites may in general produce different vaso-motor effects in different tissues, changing the effective cross-section of the capillaries and thus affecting t_p differently than T. From considerations of homeostasis, it is plausible to assume that f increases with N. Thus we have

$$f = f(N); \quad df/dN > 0. \tag{8}$$

Finally, we consider the variation of α with N. The quantity α depends primarily upon surface factors which determine the adhesiveness of the parasitized erythrocytes to the phagocytes, and upon the *saturation* of the phagocytes, i.e., upon the number of parasites contained in each phagocyte. The greater the saturation, the smaller α. If S is the saturation, then we may assume that $\alpha(S)$ decreases monotonically from $\alpha(0)$ to zero for some large value S_m of S, remaining zero for all larger values. A fair approximation which is analytically easy to handle may be obtained by assuming that α becomes zero only for infinite S, but drops rapidly with S. The surface factors will be affected by the metabolites, and therefore will be functions of N. We may put approximately, with β as a constant,

$$\alpha(N,S) = \alpha_0(N)\,e^{-\beta S}. \tag{9}$$

The saturation S is, however, itself a function of N, as is seen from the following consideration.

The total number of phagocytized parasites is equal to nS. It increases at the same rate as N decreases, that is, at a rate $\alpha n f N$.

But it decreases due to two factors; first, due to the destruction of the phagocytes which takes place at a rate bn, and second, due to the digestion of parasites by the phagocytes which takes place at a rate ηnS, η being a coefficient of proportionality. Putting

$$b + \eta = \zeta \, , \tag{10}$$

we have

$$\frac{d(nS)}{dt} = S\frac{dn}{dt} + n\frac{dS}{dt} = n(\alpha fN - \zeta S) \, . \tag{11}$$

If $f(N)$ and $\alpha_0(N)$ as well as $p(t)$ are known, then equations (4), (7), and (11) determine the quantities N, n, and S as functions of time. If the solutions of those equations show that N and S decrease sufficiently rapidly to zero while n decreases to n_0, this represents the phenomenon of recovery from the disease. If on the contrary N increases indefinitely, this represents an eventually lethal outcome. Thus the functions $f(N)$, $\alpha_0(N)$, $\theta(N)$, and $p(t)$ together with the initial value of N at the moment of infection and with the constants A, β, b, and Q, the last two being characteristic of the organism, determine in principle the course and outcome of the disease.

In the future development of the theory the functions $p(t)$, $\alpha(n)$, $f(n)$, and $\theta(N)$ should be derived from biophysical and biochemical considerations. Then, solving the system of equations (4), (7), and (11) by suitable approximation methods, we should be able to predict the course of the disease under given conditions, and check the theoretical derivation of the above four functions indirectly by the comparison of the predicted course with the observed. This, however, is yet a rather remote possibility. We shall, therefore, discuss the much more modest problem of how some of the above functions can be determined experimentally by the use of the general theory outlined above. Then we shall briefly discuss a general conclusion from the above theory in its relation to actual facts.

Determination of $p(t)$. If the division of the parasites were perfectly synchronous, then the variation of N as a function of time t would be represented by the curve $A'ABB'$ of Figure 1. Actually, due to imperfect synchronization, it is represented by a curve somewhat like $A'A''OB''B$. The curves $A'A$ and BB' represent the solution of equation (4) for $p(t) = 0$. Since far enough from the end of the interval τ, $p(t)$ is practically zero, the actual curve coincides with $A'A$ and BB' in the region AA'' and $B''B$. The curves $A''A$ and BB'' can be obtained by extrapolation of $A'A''$ and $B''B'$ until they intersect the vertical line AB, which is adjusted so that $AO = OB$. Let $z(t)$

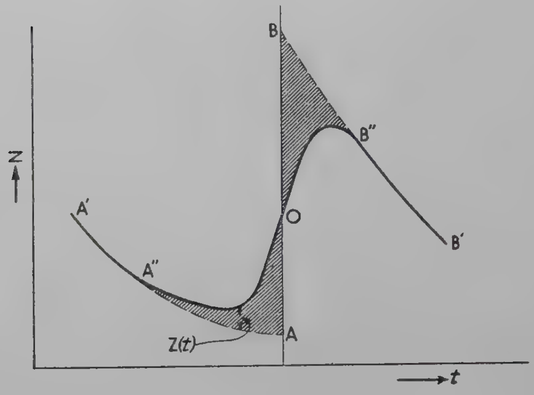

FIGURE 1

(Figure 1) denote the absolute value of the vertical distance between $A''A$ and $A''O$, or BB'' and OB''. Then $p(t) = dz/dt$, for $p(t)$ measures the deviation of the actual dN/dt from the one that would obtain if $p(t) = 0$. Thus we can graphically construct $p(t)$, and then determine by standard methods the coefficients a_i and b_i of the Fourier expansion (1).

Determination of $\alpha_0(N)$ *and* n. A direct determination of n apparently presents great difficulties, and very little is known quantitatively about its variation with time. However, there is evidence that the rate of increase of n with time is much slower than the rate of increase of N (Knisely, 1944). It is plausible to assume that $\alpha_0(N)$ and $f(N)$ are also relatively slowly varying functions of the form,

$$\begin{gathered} \alpha_0(N) = \alpha_0 + \alpha_1(N)\,;\ d\alpha_1/dN > 0\,, \\ f = f_0 + f_1(N)\,;\ df_1/dN > 0\,. \end{gathered} \tag{12}$$

Under these conditions we may make a rough estimate of the average value $\overline{\alpha f n}$ of $\alpha f n$ for the period of one asexual cycle.

Let N_1 represent the peak value of N at the end of an interval τ, this peak value being graphically corrected for perfect synchronization by extrapolating the line $B'B''$ in Figure 1. In other words, let N be the ordinate of the point B. Let N_2 be a similar quantity for the next interval. During the interval τ, the number N_1 has, according to equation (4), dropped to $N_1 e^{-\overline{\alpha f n \tau}}$ and then suddenly increased M times. Hence

$$N_2 = MN_1 e^{-\overline{\alpha f n}\tau}, \tag{13}$$

or

$$\overline{\alpha f n} = \frac{\log\left(M\dfrac{N_1}{N_2}\right)}{\tau}. \tag{14}$$

Thus the knowledge of M, τ, and of two consecutive corrected peak values of N gives us $\overline{\alpha f n}$. For a very rough estimate, actual uncorrected peak values may be used.

If α, f, and n were constant; then N_2/N_1 would be constant for any two consecutive peaks. By observing the variation of N_2/N_1 as a function of the varying average N in the course of the disease, we may make a rough estimate of the variation of $\overline{\alpha f n}$, and hence of $\alpha f n$, with N.

Determination of $\alpha(N)$. The quantity α is the probability that a parasite will be removed by a particular phagocyte in a unit of time. Hence $\alpha n t_p$ is the probability that a parasite will be removed by an organ containing n phagocytes. Suppose we inject in a non-infected organism a number N_a of parasites into the artery supplying a phagocytic tissue, say the splenic artery, and find that N_v parasites are recovered in the blood of the corresponding vein. Then

$$\alpha(N_a) n t_p = \frac{N_a - N_v}{N_a}, \tag{15}$$

or

$$\alpha(N_a) = \frac{N_a - N_v}{n t_p N_a}. \tag{16}$$

If n can be determined by direct observation, then, t_p being known, we can determine the values of α for different values of N. If, however, as remarked above, n varies rather slowly with time, then in experiments of that kind n will be practically constant, having the value n_0. Even if the latter is not known, in this way we can determine $\alpha(N)$ up to a constant factor of proportionality.

A different procedure may also be used, especially for small values of N. Suppose that it has been determined that in a certain fraction of cases, say 50%, the disease develops when a certain number N_h of parasites is injected into the vein of a phagocytic organ of a healthy animal. Suppose now that various numbers N_a of parasites be injected into the corresponding artery, and it is found that a certain value $N^* > N_h$ will produce the disease in 50% of all cases. This means that of N^* parasites, N_h escaped into the vein, while $N^* - N_h$ were destroyed in the tissue. Hence we have

$$\alpha = \frac{N^* - N_h}{nt_pN^*}. \tag{17}$$

This gives the value of $\alpha(N)$ for $N = N^*$. If we use different values of N_h and N^*, corresponding to different percentages of incidence of the disease after injection, we may thus gain an idea about the form of the function $\alpha(N)$.

The Determination of $n(t)$. The procedure of injecting N_a parasites into an artery of a phagocytic organ and of determining the number N_h left in the corresponding vein may be used not on a healthy animal, but on an animal with an advanced stage of the disease when a certain number N of parasites is already present in the blood stream. Such determination may be made at definite times t, from the initial infection of the animal. The total number $N(t)$ of the parasites already present in the blood stream may also be determined. Let the same amount N_a always be injected, and denote by a prime the amount recovered in the vein of an already infected animal. Similarly to expression (16) we now have

$$\alpha_0(N)n(t) = \frac{N_a - N'_v}{N_a t_p}. \tag{18}$$

where N is the number of parasites just previous to the injection. Or, dividing (18) by (16), we have

$$\frac{\alpha(N)n(t)}{\alpha(N_a)n_0} = \frac{N_a - N'_v}{N_a - N_v}. \tag{19}$$

If from experiments on non-infected animals we know α as a function of N, then, since in the experiments with already infected animals, N is known for any t, relations (18) and (19) enable us to determine $n(t)$. If direct observations of n are possible, the theory can be checked by comparing the directly observed values of $n(t)$ with those found by means of equations (16), (18), and (19).

If the function $N(t)$ is determined by direct count of parasites, and thus is known, then equation (7) may be integrated, giving,

$$n = n_0 + e^{-bt} \int_0^{t-t_1} e^{bt} A\,\theta(N)\,dt. \tag{20}$$

With known $n(t)$ and $N(t)$, either equation (7) or equation (20) may then be used for the determination of the function $\theta(N)$.

While all the above suggested procedures may meet with certain practical and technical difficulties, yet it is important that in principle even this outline of a theory suggests experimental methods for the determination of the important functions $\alpha(N)$, $f(N)$, $n(t)$, and $\theta(N)$, which largely determine the course of the disease. Once they are determined, we may study effects upon those functions of different physical and chemical agents.

Some General Consequences. The periodicity of $p(t)$ gives an "oscillatory" character to the whole course of the disease, the value of N increasing sharply at regular intervals, and then dropping again more slowly until the next increase. The final outcome is largely (though not solely) dependent on whether the general over-all trend of N is to increase or to decrease. To study this general trend, we may replace $p(t)$ by an average constant value p, obtained by averaging $p(t)$ over the interval τ. We shall again consider the case that f and n are varying relatively slowly, so that over not too long a period of time they may be replaced by their averages $\overline{f}$ and $\overline{n}$. Then, putting

$$y = \log N\,, \tag{21}$$

we obtain instead of equation (4),

$$\frac{dy}{dt} = \overline{p} - \alpha(y)\overline{fn}. \tag{22}$$

Considering the case that the saturation S is zero, we may put as a first approximation,

$$\alpha(y) = \alpha_0' + \alpha_1' y\,. \tag{23}$$

Integrating equation (22), we find, denoting by y_0 the value of y for $t = 0$:

$$y = \frac{\overline{p} - \alpha'_0\,\overline{fn}}{\overline{fn}\,\alpha'_1} + \left(y_0 - \frac{\overline{p} - \alpha'_0\,\overline{fn}}{\overline{fn}\,\alpha'_1} \right) e^{-\overline{fn}\alpha'_1 t}. \tag{24}$$

If into an organism initially free of parasites, in which therefore $S = 0$, we inject at the time $t = 0$, N_0 parasites, then, if $N_0 < N_e = (\overline{p} - \alpha'_0\overline{fn})/\overline{fn}\alpha'_1$ and $\overline{p} > \alpha'_0\overline{fn}$, the number of parasites will asymptotically increase towards the equilibrium value N_e. If $N_0 > N_e$, the number will decrease towards N_e. Due to the variability of $\overline{f}$ and $\overline{n}$, the equilibrium value N_e is not constant, but itself varies slowly with time. (Figure 2, full lines.)

If, however, $\overline{p} < \alpha'_0\overline{fn}$, then y (or N) will never increase. (Figure 2, broken lines.) Hence, a necessary condition for a disease to occur and continue, in terms of the present simplified theory is that

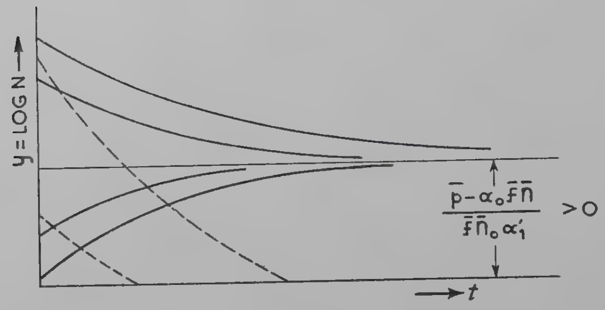

FIGURE 2

$\overline{p} > \alpha'_0\overline{fn}$. Since, as we have said above, at the beginning of the disease we have with good approximation, $\overline{f} = f_0$; $\overline{n} = n_0$, hence the above condition becomes $\overline{p} > \alpha'_0 f_0 n_0$. This suggests that if $\overline{p}$ could be reduced sufficiently, or if α_0 and n_0 could be increased sufficiently for a given individual, then we would say that the individual is immune. Note that $\overline{p}$ can be reduced by reducing the merozoite number M or by increasing τ.

Now let us consider the effects of the saturation S. If n varies very slowly, we can neglect in equation (11) the term with dn/dt. Introducing also the expression (9) with (11), we now find

$$\frac{dS}{dt} = \alpha_0(N)\overline{f}Ne^{-\beta s} - \zeta S. \qquad (25)$$

It is readily seen that S approaches in equilibrium value S_e, which is the root of the equation

$$\alpha_0(N)\overline{f}Ne^{-\beta s} - \zeta S = 0. \qquad (26)$$

This equilibrium is stable because for $S < S_e$ the expression (26) is positive, while for $S > S_e$ it is negative. Moreover, since $\alpha_0(N)$ increases with N, it can be readily seen graphically that S_e increases with N also.

Consider now a hypothetical case in which the number of parasites in an organism has somehow been maintained at an approximately constant level, N, so that S has reached a constant level, and assume that the parameters in equation (25) are such that S also varies more slowly than N when the latter is suddenly changed. If we now inject a given number N^* of parasites, it will vary according to equation (22) into which, however, equation (9) must now be introduced. Considering that expression (23) now stands for $\alpha_0(N)$, we now have:

$$\frac{dy}{dt} = -\,(\alpha'_0 + \alpha'_1 y)\,\overline{fn}e^{-\beta s}, \tag{27}$$

or, integrated

$$y = -\frac{\alpha_0'}{\alpha_1'} + \left(y_0 + \frac{\alpha_0'}{\alpha_1'}\right)e^{fn\alpha'_1 te^{-\beta S}}. \tag{28}$$

Equation (28) shows that if we start with $\bar{N} = 0$, $S = 0$, we shall find that after injection the number of parasites will decrease relatively rapidly, (Figure 3, solid line) since $e^{-\beta s} = 1$ and the coefficient of t in the exponent is large. If we start with larger values of $\overline{N}$ so that $S > 0$, then y (or N) will decrease after the injection much more slowly. (Figure 3, dash line.) For still larger $\bar{N}$, we shall have a still slower decrease. (Figure 3, broken line.)

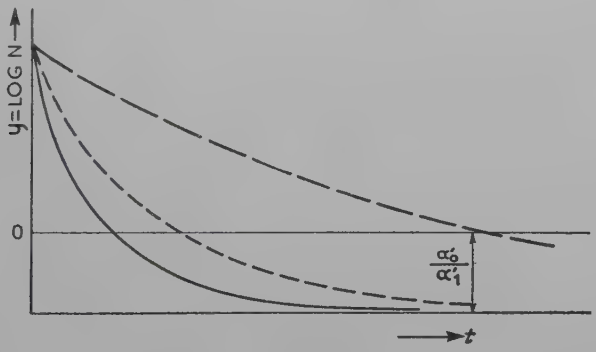

FIGURE 3

From such experiments it should be possible to find something about the rate of phagocytosis as a function of the saturation S. We should expect a high rate of removal after injection in a healthy organism, which should not be the case with a sick organism.

The above considerations suggest an explanation for the apparent high rate of removal of parasites in a newly infected host and the low rate in a diseased host necessary to maintain the disease.

The author is indebted to Professor M. Knisely for a discussion of the paper and for valuable suggestions.

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LITERATURE

Knisely, M. 1944. Unpublished. Personal communication to the author.

Taliaferro, W. H. and P. R. Cannon. 1936. "The Cellular Reactions During Primary Infections and Superinfections of Plasmodium Brasilianum in Panamanian Monkeys." *Journal of Infectious Diseases*, 59, 72-125.

Taliaferro, W. H. and H. W. Mulligan. 1937. "The Histopathology of Malaria with Special Reference to the Function and Origin of Macrophages in Defense." *The Indian Medical Research Memoirs*, 29, 1-138.

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SIMPLIFIED EQUATIONS FOR THE DISTRIBUTION OF CHLORIDE IN BODY WATER

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According to the theory of Boyle and Conway, chloride leaves the extracellular fluid to enter cells, particularly muscle, when the plasma potassium concentration K rises. Simplified equations are presented to describe in terms of K the distribution of chloride expected when the quantity of the salt Kp in the body fluids changes in health and disease.

Notation.

Volumes are given in liters of water according to the phase occupied: I, intracellular; E, extracellular; $W = I + E$.

Total content of *ions* in both phases of animal or tissue, in milliequivalents, is designated by boldfaced type, as $\mathbf{Cl}$.

Concentrations of diffusible ions in milliequivalents per liter of water in the phases are expressed in *italics*, intracellular values being marked by the subscript 1, as Cl_1. It is assumed that concentrations represent activities.

Symbols for concentrations and contents.

K = potassium: extracellular, K; intracellular, K_1 ($''K_1$, if associated with Y^-; $'K_1$, if associated with diffusible anions).

N = those non-diffusible cations in E associated with *diffusible* anions.

Cl = chloride.

p = diffusible anions of any species univalent, in quantity set arbitrarily equal to $K\ W$, or to $'K_1 I + K\ E$.

a = sum of diffusible anions other than Cl and p.

$n = Cl + a$.

$d = Cl + a + p$.

Constants, since E and I, $\mathbf{Cl}$ and $\mathbf{a}$ are held constant.

For n: $A = \mathbf{n}/E$; $C = \mathbf{n}/I$; $L = \mathbf{n}/W$.

For Cl: $B = \mathbf{Cl}/E$; $D = \mathbf{Cl}/I$; $M = \mathbf{Cl}/W$.

Theory. Many features of the Boyle and Conway theory of the distribution of electrolytes in muscle are illustrated in Figure 1. The organic radical Y^- and the inorganic N^+ are by some mechanism restricted to the phase I or E indicated. N is mostly sodium; part of Y

may include phosphoric acid esters. These ions attract diffusible ions of opposite charge: N attracts Cl and other anions a and p; Y attracts mostly K, most of which may be ionized. These complexes account for the effective osmotic pressures of the respective phases. These pressures remain equal since the surface S exerts no tension.

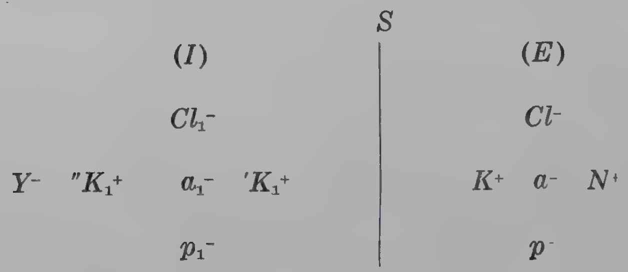


FIGURE 1

A unique feature of the theory is that the anions Cl, a, and p of the cell water exist at a concentration such that their sum approximates the value of K in the extracellular fluid. It is assumed that the potassium salt of these anions spreads throughout the free water of I and E with concentrations in the two phases equal, $'K_1$ being equal to K as shown in Figure 1.

These potassium salts have no osmotic control over body water. They diffuse passively along with water as it is moved by other effective osmotic forces: into the cells in water intoxication, out of the cells in the dehydration of thirst. In dehydration much of the potassium lost to the urine in excess of that accompanying the nitrogen derived from tissue destruction is probably from this source (see data of Elkinton and Winkler, 1944).

Objection has been raised to studying these ionic equilibria as did Boyle and Conway in muscle immersed in artificial and unphysiological media. Yet whereas in such media the equations can be simplified because the external concentrations can be kept constant through the buffering capacity of an infinite volume, application to live animals would seem complicated by interacting changes in concentration between phases E and I. So far from this being a handicap, it is only by meeting it, as in the equations to be presented, that we realize the possibility of testing the ideas of Boyle and Conway through changes in plasma concentrations and of thus avoiding the difficulty of measuring cell concentrations through such indirect methods as the inulin-space concept.

The Relation of Cl_1 to K. The fundamental equation underlying these developments can be derived in at least two ways. The one, a special case of the Donnan equilibrium for a membrane with ion pores, follows directly from Boyle and Conway. From their general equations (5) and (6), $K_1Cl_1 = K\ Cl$ and $K_1d_1 = K\ d$. Division of one equation by the other yields $Cl_1/d_1 = Cl/d$. And substitution from their special equation (23), $K = d_1$, leaves

$$Cl_1 = (Cl/d)K. \tag{1}$$

Thus for equation (1) to obey Donnan concepts not only must $K = d_1$, but also must $K_1 = d = N + K$. This is true in immersed frog muscle over a wide range of changes of concentrations of K in the external medium (Boyle and Conway, Table 7). The analytical values for K_1 in fresh muscle from laboratory animals as published over the last decade approximate this value. This implies that the average valence of Y is one. It is calculated to be 1.09 for the frog and 0.805 for the dog (Dean, 1941; pp. 336 and 344). Equation (17) from Dean, $d_1 = K(m + 1)/2\ m$, m being the valence of Y, is the exact relation when the mol fraction of K in the external medium is small as it must be because of the limitations of toxicity. Equation (1) fits the white rat with a high degree of statistical significance (Wilde, 1943) even though K_1 exceeds d markedly.

A second type of derivation for equation (1) is a natural extension of the "visual" approach presented under *Theory*. The distribution of the diffusible anions in the two phases is predicted by statistical mechanics. The probability Cl_1/d_1 that a chloride ion will be associated with a given $'K_1$ ion in the cell is equal to the probability of the analogous association outside the cell between chloride and $(N + K)$. Since the concentration of all diffusible anions inside is equivalent to $'K_1 = K$, we write $Cl_1 = (Cl/d)K$. If the activity coefficients of the anions differ considerably inside and outside the cell, the use of a ratio Cl/d in which chloride is predominant in numerator and denominator minimizes the error that such differences of activity impose upon prediction.

An equation so derived is more general in that it applies to situations in addition to the special Donnan case described. It may, for instance, fit some of the theories reviewed by Steinbach (1940, p. 251). However, since these have their difficulties, particularly in explaining osmotic relations, further discussion seems futile in a paper of this length. These developments are presented as a guide for testing the relation between plasma potassium and intracellular or extracellular chloride.

Algebraic manipulation proves the identity, $Cl/d = (Cl\ E +$

$Cl_1I)/(dE + d_1I) = Cl/d$. Substitute Cl/d, using $d = n + p$, into equation (1), which when multiplied by W/W gives

$$Cl_1 = \frac{Cl/W}{n/W + p/W} K. \qquad (2)$$

Consider the special system in which during the development and growth of the animal, or in experiment or in disease, K and p are added together in equal quantities as the salt Kp. Whether p is a single species of anion does not matter as long as it is diffusible, univalent, and of uniform activity. The potassium K considered here is only that appearing with p beginning with the origin of the animal, or on mixing in the adult only that potassium associated with diffusible anions inside or outside the cell, that is, $K = K_1I + KE$. Thus since $p = K$, $p/W = K/W = K$. Substituting this into equation (2), with Cl and n held constant, we write

$$Cl_1 = \frac{M}{L + K} K. \qquad (3)$$

Approximate values for the constants for the entire dog have been estimated from the literature. The lower curve of Figure 2 is drawn from $Cl_1 = 31.4\,K/(34.3 + K)$.

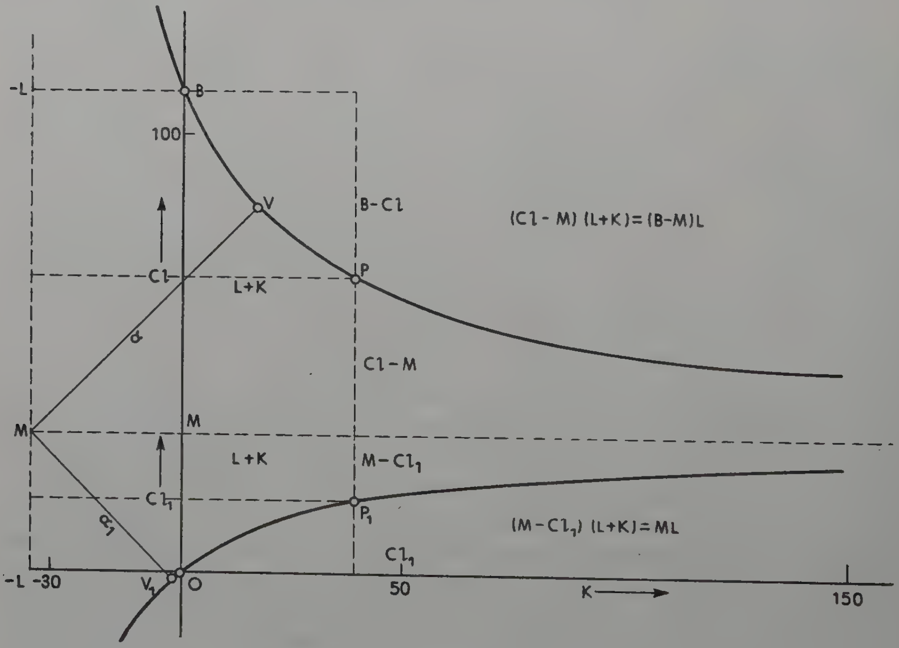


FIGURE 2

Further analysis reveals that the curve is an equilateral hyperbola. If $K \to \infty$, $Cl_1 \to$ the limit $Cl_1 = Cl = M$. If $K = -L$, $Cl_1 = -\infty$. From the derivative,

$$\frac{d(Cl_1)}{dK} = \frac{M\,L}{(L+K)^2}, \tag{4}$$

the slopes at these respective values are 0 and ∞. The asymptotes, $Cl_1 = M$, $K = -L$ are predicted (Figure 2). Visual inspection of the lower curve, on consideration of the conventional form $x_1y_1 = x_2y_2 = a^2/2$, gives

$$(M - Cl_1)(L + K) = M\,L, \tag{5}$$

in which the left member results from substitution from the variable point P_1, taking account of the fact that the asymptotes cross at $(-L, M)$ rather than at the origin, and in which the right member results from substitution of the special point, the origin, which gives the constants. It is seen that a_1 (from the conventional equation) $= \sqrt{2\,M\,L}$. Conversion of equation (5) into equation (3) confirms the analysis.

The Relation of Cl to K. Write $Cl = (Cl/d)\,d$. Then by substitution of $d = N + K$,

$$Cl = (Cl/d)(N + K). \tag{6}$$

In this form equation (2) is a meaningless expression of the equality between positive and negative radicals in extracellular fluid that holds in any theory. However, in the development to follow a useful relation will appear between Cl and K.

Continuing the development as with equation (2), write

$$Cl = \frac{Cl/W}{n/W + p/W}(N + K) = \frac{M(N+K)}{L+K}. \tag{7}$$

For this to follow Donnan relations, because of the substitution $p/W = K$, d_1 must again equal K as for equation (1).

Equation (7) is an equilateral hyperbola with the same asymptotes as equation (5), and from the upper curve of Figure 2,

$$(Cl - M)(K + L) = (B - M)L; \tag{8}$$

$a = \sqrt{2(B-M)L}$. Equation (8) converts to (7) on use of the identity $BL = MA$. While the two hyperbolas (5) and (8) have the same asymptotes, their foci are at different distances from the center. They are typical conjugates only when $2M = B$, when $E = I$, a condition not normally found in mammals.

The Relation of Cell Chloride to Extracellular Chloride. Granting homogeneity of chloride in E and I, regardless of the mechanism of chloride transfer, one writes $Cl\,E + Cl_1 I = \mathbf{Cl}$. Whence,

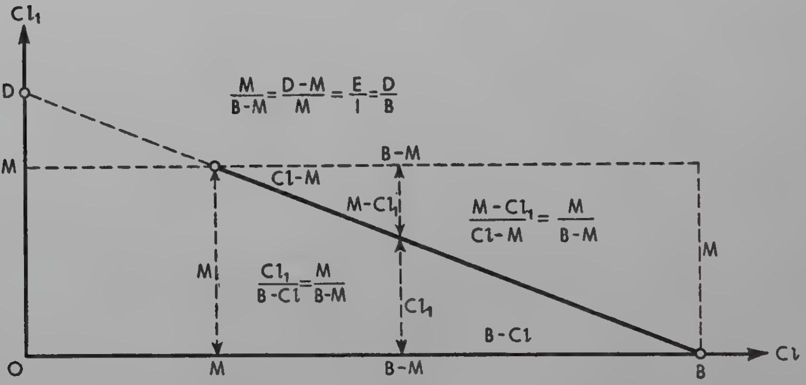
$$Cl_1 = \mathbf{Cl}/I - E/I\,Cl = D - E/I\,Cl; \tag{9}$$

or

$$Cl = \mathbf{Cl}/E - I/E\,Cl_1 = B - I/E\,Cl_1 . \tag{10}$$

These convert to either of the slope equations derived geometrically in Figure 3. Also dividing relation (5) by relation (8), we write

$$(M - Cl_1)/(Cl - M) = M/(B - M). \tag{11}$$



Cl_1
D
M
$\frac{M}{B-M} = \frac{D-M}{M} = \frac{E}{I} = \frac{D}{B}$
B-M
Cl-M
$M-Cl_1$
$\frac{M-Cl_1}{Cl-M} = \frac{M}{B-M}$
M
M
$\frac{Cl_1}{B-Cl} = \frac{M}{B-M}$
Cl_1
B-Cl
O
M
B-M
B
Cl

FIGURE 3

The Relation between the Three Variables. Division of equation (3) by equation (7) yields

$$Cl_1/Cl = K/(N + K). \tag{12}$$

Variation of K with $\mathbf{p}$ *Held Constant.* If K varies without changing $\mathbf{p}$, the constancy of $\mathbf{p}/W$ eliminates K from the denominators of equations (3) and (7). Linearity results except for complicating volume changes avoided when K varies through addition of $\mathbf{Kp}$. If K is substituted in part for N (Wilde, 1943), the hypotonic N allows I to swell at the expense of E. Suitable calculations show that $(N + K)$ rather than N of expression (7) is a constant. The concentrations Cl, d, and p remain constant, while Cl_1 is a true linear function of K.

Applications. Equations (3) and (7) may apply to entire animals or to tissues excised *after* equilibration. Any anion supposedly diffusible may be substituted for Cl, for instance HCO_3, SCN, Br, etc. Application to tissues, as muscle, is simpler since the constants L and M can be measured directly. Values of Cl_1 calculated from expression (3) may be compared with Cl_1 estimated by some analogue of inulin-space. Cl_1 calculated from equation (12) may also be so compared. In another approach, since the reciprocal of expression (3) is linear,

$$(1/Cl_1) = 1/M + L/M(1/K), \tag{13}$$

the constants may be estimated by least squares.

Estimation of the constants for equation (7) is more involved, especially if applied to an entire animal, for the behavior of chloride in different tissues may vary. However, the equation is very useful for predicting changes in plasma chloride in terms of plasma potassium when the latter increases in disease. For instance, from the equation plotted as the upper curve of Figure 2, $Cl = 31.4\ (120 + K)/(34.3 + K)$, it can be calculated that if in such conditions as shock, hemorrhage, or renal disease the plasma potassium rises from 5 up to 10 milliequivalents per liter of water, presumably as $\boldsymbol{Kp}$ appears in the system, the plasma chloride may fall from 100 to 92 milliequivalents per liter. No other explanation has been offered for such changes, which must represent a redistribution of chloride since none of the ion is lost to the exterior.

If in the live animal only muscle participates in these relations, then I is reduced one-half and $-\Delta Cl$ correspondingly. Also any exchange between p and corpuscular Cl will reduce the change. On the other hand, dehydration of the E phase of the animal before injection of the salt Kp, in that the E/I ratio is lowered, will increase the experimental drop in plasma chloride.

LITERATURE

Boyle, P. J. and E. J. Conway. 1941. "Potassium Accumulation in Muscle and Associated Changes." *Jour. Physiol.*, 100, 1-63.

Dean, R. B. 1941. "Theories of Electrolyte Equilibrium in Muscle." *Biol. Symposia*, 3, 331-348. The Jaques Cattell Press, Lancaster, Pa.

Elkinton, J. R. and A. W. Winkler. 1944. "Transfers of Intracellular Potassium in Experimental Dehydration." *Jour. Clin. Invest.*, 23, 93-101.

Steinbach, H. B. 1940. "Electrolyte Balance of Animal Cells." *Cold Spring Harbor Symp. Quant. Biol.*, 8, 242-254.

Wilde, W. S. 1943. "Entrance of Chloride with Potassium into Live Rat Muscle Fibers—*Cl*-Space Error." *Science*, 98, 202-203.

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ON THE FORM AND STRENGTH OF TREES:

PART I. THE TRUNK

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The theory of strength of materials and known experimental relations between the strength and the specific gravity of green wood are used to derive relations between some geometric characteristics of the tree.

1. Some fundamental facts. N. Rashevsky (1943) has shown that a theory of form of plants can be based on concepts of metabolism and mechanical strength. It is the purpose of the present paper to indicate the contributions to be expected from the theory of the strength of materials. To derive numerical formulae, use is made of the results obtained by the Forest Products Laboratory of the U. S. Department of Agriculture on the elastic and strength properties of wood. These experiments are so exhaustive and cover such a wide variety of tree species that their use for theoretical purposes appears justified. The relations that we will need are the following (Markwardt-Wilson, 1935, pp. 36-40):

For *compression parallel to the grain,* the maximum strength σ_c is given by

$$\sigma_c = 473G \text{ kg cm}^{-2}, \tag{1}$$

and the modulus of elasticity E_c is given by

$$E_c = 204600G \text{ kg cm}^{-2}. \tag{2}$$

For *static bending,* the maximum strength σ_b is given by

$$\sigma_b = 1237G^{5/4} \text{ kg cm}^{-2}, \tag{3}$$

and the modulus of elasticity E_b is given by

$$E_b = 165900G \text{ kg cm}^{-2}, \tag{4}$$

where G is the specific gravity of oven dry wood based on the volume in green state. The units are kilograms and centimeters throughout the paper, unless otherwise stated. Equations (1) to (4) are results of tests obtained on green wood; they are applicable to live trees, at least for most species grown in this country, because these species do not show differences in mechanical properties of sapwood, which consists mostly of living cells, and heartwood, containing dead cells only (Markwardt-Wilson, 1935, pp. 41,42).

In calculating the weight of the tree we have to take into account its *humidity content*. Therefore, we will put for the average specific weight of the tree, $w = mG/1000$ kg cm^{-3}, where the factor m may vary between about 1.3 and 2.5 (Markwardt-Wilson, 1935, p. 7). For the actual compressive stress in the tree, when no external forces are acting, we shall write σ_c/f, where f, a *safety factor,* is greater than one.

2. A simple geometric model of a tree. Consider the trunk as a circular cone, and take into account the weight of the branches by multiplying the specific weight of the trunk by the ratio $\rho = B/T$, where B is the weight of all the branches and T the weight of the trunk (Greenhill, 1881, pp. 69, 70; Olsson, 1942, pp. 173, 174). If we treat the trunk as a simply compressed column (Timoshenko, 1940, p. 4), the calculation of the stress at the base of the trunk gives $m(1 + \rho)fHG = 30\ \sigma_c$, where H is the height of the tree in meters. Taking into account expression (1), we obtain from here

$$m(1 + \rho)fH = 14190\,. \tag{5}$$

Since $f > > 1$, equation (5) gives a *limitation for the height* of the tree which is seen to be independent of the specific gravity that is of the species of the tree as well as of the size of the base. To see the order of magnitude of f at its possible lower limit, consider a case of a very tall tree, a sequoia for instance: $H = 100$ meters, $m = 2$, $\rho = 1$. We find $f = 35.5$.

For a column of the size of a tree the conditions of *elastic stability* are likely to be more important than those of compressive strength (Timoshenko, 1936, pp. 64, 65; 1941, pp. 184-186). For a circular cone under the action of its own weight, the maximum height H_1 compatible with elastic stability is (Greenhill, 1881 pp. 69, 70): $H_1 = (7.63E_b\ r^2/w)^{1/3}$, where r is the radius of the base. Using relation (4), we thus obtain

$$[m(1 + \rho)/r^2]^{1/3}\,H_1 = 1082\,.$$

One may call *stability of the tree* the ratio $\xi = (H_1 - H)/H_1$ where H is the actual height of the tree. For a very high tree, for instance a sequoia sempervirens at its upper limit of size (Rehder, 1940, p. 48), $H = 110$ meters, $r = 4$ meters, so that by assuming $m = 2$, $\rho = 1$, we get $H_1 = 370$, $\xi = 0.7$.

3. The effect of eccentricity. One may take into account the eccentricity of the tree with respect to its base by calculating the maximum compressive stress at the base due to the combined effect of compression and bending. We assume the base to be circular of radius r, and εr the horizontal distance of the center of gravity of the tree from the center of the base. Then the maximum compressive stress at the base is (Timoshenko, 1940, pp. 230, 231): $\sigma = \sigma_c(1 + 4\,\varepsilon)$, where σ_c is the compressive stress for a perfectly symmetric tree of the same weight and base. It is seen that the eccentricity increases the stress quite substantially. This is the reason why high trees are in general more symmetric.

4. A model of a tree of maximum strength. Instead of assuming the tree is a cone, there is a possibility of deriving its shape from a general principle, according to which the material from which a plant is made is distributed in such a manner as to give a maximum strength. This principle was widely discussed by S. Schwendener (Holtermann, 1909; Fischer, 1904, pp. 119, 120) who gave actual evidence for its occurrence in the botanical world. We limit ourselves here to applying this principle to the trunk, which we treat as a compressed column. The principle of maximum strength is alone not sufficient to determine the shape. We add the condition of maximum height which is biologically justified at least in the case of closely grown trees. Since we keep out of consideration the phenomena of growth, we may assume the amount of material involved to be an assigned quantity. Then it is clear that the condition of maximum strength and maximum height implies that the stress be the same in each cross-section of the trunk, that is, that the trunk be of *equal strength* (Timoshenko, 1940, pp. 17, 18).

We may take into account the weight of the branches in the same way as previously. Then if $a(z)$ is the area of the cross-section of the trunk at a distance z from the base, the condition of equal strength gives:

$$f(1 + \rho)w \int_z^H a(z)\,dz = \sigma_c\, a(z)\,. \tag{6}$$

The differentiation of this with respect to z gives $d\log a/dz =$ const. which may be easily integrated, but such an integral satisfies equation (6) only if the height H of the tree is infinity. This inacceptable conclusion is a consequence of the assumption that we made, that is, that the cross-section a is a differentiable function of the distance z. We have to abandon such conception of a smooth profile of the tree trunk and bring ourselves closer to the actual shape of the tree.

Number the branches of the tree progressively starting, for instance, from the top: $1, 2, \cdots, i, \cdots n$. Assume that at the trunk base no branches exist. Call the i-th trunk element that one which lies between the branches i and $i + 1$. Let each i-th trunk element be bounded by two horizontal areas: a_i at the top and a_i' at the bottom. Two consecutive trunk elements are considered in direct connection with each other, so that the areas a_i' and a_{i+1} are superimposed with a_i' internal to a_{i+1}. Therefore, at the connection of two trunk elements the cross-section of the trunk has a discontinuity. We imagine that at this discontinuity a branch is attached to the trunk. Let H_i be the height of the i-th trunk element, T_i its weight, and B_i the weight of the i-th branch. Put $a_i/a_{i+1} = \alpha_i$, $t_i = fT_i/\sigma_c$, $b_i = fB_i/\sigma_c$, $b_i/t_i = \rho_i$, $1 + \rho_i^{-1} = R_i$, $\alpha_i/\rho_{i+1} = A_i$, and with H_i in meters,

$$h_i = fwH_i/\sigma_c = mfH_i/4730 ; \tag{7}$$

t_i and b_i have the dimensions of areas, h_i is dimensionless. The ratio ρ_i may be called the *ramification,* and α_i the *cross-sectional reduction* of the i-th element. We apply now the principle of equal strength to each trunk element. From the theory of strength of materials we have the following relations (Timoshenko, 1940, pp. 17, 18):

$$a_i = a'_{i-1} + b_i , \quad a_i' = a_i \exp h_i , \quad t_i = a'_i - a_i , \tag{8}$$

the quantities with negative subscripts are here by definition $= 0$. It may be noted that our present tree model must have a branch on its top because otherwise we would get $h_1 = \infty$. The elimination of a_i' and a'_{i-1} between equations (8) gives

$$t_i = a_i \exp h_i - a_i , \quad b_i = a_i - a_{i-1} \exp h_{i-1} ,$$

which divided side by side leads to a dimensionless relation between the heights of two adjoining trunk elements;

$$\exp h_i = R_i - A_{i-1} \exp h_{i-1} . \tag{9}$$

From relation (9) we have

$$\exp h_2 - \exp h_1 = R_2 - R_1 - A_1 \exp h_1 . \tag{10}$$

If we assume that the height of the trunk elements increases from the top to the bottom, we have $h_2 > h_1$, and from expression (10) $R_2 > R_1$ or $\rho_2 < \rho_1$, that is, the ramification is smaller for the second than for the first trunk element. This agrees with the fact that the second trunk element must provide for a metabolic flow not only to its own branch 2, but also to the top branch 1. By this consideration of metabolic flow, it is justified to assume that all ρ_i decrease from the top to the bottom. Since each side of expression (10) is > 0, we have also $R_2 - R_1 > A_1$ or $\alpha_1 < 1 - (\rho_2/\rho_1)$, that is, $\alpha_1 < 1$ which is intuitive too.

As important as the mechanical strength is for the life of a plant, it is not the only factor affecting its shape. Therefore, equations (8) must be completed by some mathematical expressions of metabolism and growth, which would make it possible to relate to each other the various trunk elements as well as the branches to the trunk. It is possible, however, to derive from equation (9) a relation between certain *geometric characteristics of the tree as a whole* without any additional hypothesis. In general, h_i's are sufficiently small [cf. equation (7)] so that $\exp h_i = 1 + h_i$. This means the exponential profile of each trunk element is approximated by a suitable truncated cone. Using this approximation, and adding all the equations (9) to each other, we get

$$h\,\rho^* + (h - h_n + n - 1)\,\alpha^* = n \tag{11}$$

where $h = \sum_1^n h_i$ represents the height of the whole tree;

$$n/\rho^* = \sum_1^n 1/\rho_i\,,\; A^* = \sum_1^{n-1} A_i(1 + h_i)/\sum_1^{n-1}(1 + h_i),\; \alpha^* = A^*\rho^*\,,$$

and ρ^* is harmonic average of all ramifications and may be called the *ramification of the tree.* A^* is a weighted average of the coefficients A_i's, therefore α^* may be called the *average cross-sectional reduction of the tree trunk.* Since one may expect $\alpha^* < 1$, we get from relation (11) a condition for ρ^* which is independent of n, that is $(1 + \rho^*)\,h > 1 + h_n$, or by equation (7);

$$\rho^* > 4730\,(mHf)^{-1} + H_n H^{-1} - 1\,, \tag{12}$$

where H and H_n are in meters.

For instance, if $H = 100$, $H_n = 2$, $m = 2$, $f = 35$, condition (12) is satisfied for any ρ^*. If, however, $H = 25$ m, ρ^* must be at least about 1.8, unless $f > 35$. Qualitatively the condition (12) is intuitive: small trees (i.e. small H) which do not have heavy branches (small ρ^*) have a high safety factor f. In expression (11), n is very large with respect to h, so that α^* is close to 1, which agrees also with qualitative observations of the trees.

LITERATURE

Fischer, O. 1904. "Physiologische Mechanik". *Encykl. d. math. Wiss., IV*.8, 62-126.

Greenhill, A. G. 1881. "Determination of the Greatest Height Consistent with Stability that a Vertical Pole or Mast Can Be Made, and of the Greatest Height to Which a Tree of Given Proportion Can Grow." *Proc. Cambridge Philos. Soc.*, 4, part II, 65-73.

Holtermann, C. 1909. *Schwendener's Vorlesungen über mechanische Probleme der Botanik.* Leipzig.

Markwardt, L. J. - Wilson, T. R. C. 1935. *Strength and Related Properties of Woods Grown in the United States.* U. S. Dept. of Agriculture, Technical Bulletin No. 479.

Olsson, G. R. 1942. "Elastische Knickung gerader Stäbe von exponentiell veränderlichem Querschnitt unter dem Einfluss ihres Eigengewichtes." *Ingenieur-Archiv*, 13, 162-174.

Rashevsky, N. 1943. "On the Form of Plants and Animals." *Bull. Math. Biophysics*, 5, 69-73.

Rehder, A. 1940. *Manual of Cultivated Trees and Shrubs.* New York: MacMillan, 2nd Ed.

Timoshenko, S. 1936. *Theory of Elastic Stability.* New York: McGraw-Hill.

Timoshenko, S. 1940. *Strength of Materials.* Part I. New York: Van Nostrand.

Timoshenko, S. 1941. *Strength of Materials.* Part II. New York: Van Nostrand.

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A CONTRIBUTION TO THE MATHEMATICAL BIOPHYSICS OF VISUAL PERCEPTION AND AESTHETICS

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In continuation of previous studies of the mathematical biophysics of visual perception in relation to the aesthetic evaluation of visual patterns, an expression for the total intensity of excitation in a discriminating center as a function of the intensity of the peripheral stimulus is derived. This expression is applied to the case of aesthetic judgments of similar polygons of different sizes. The theoretical conclusions are tested experimentally by use of standard psychological scaling methods. The theoretical predictions are found to be in agreement with the experimental results.

In a previous paper (Rashevsky, 1942) we pointed out the importance of the function $I(S)$, introduced by A. S. Householder (1939) for the mathematical biophysics of perception. Previous notations (Rashevsky, 1940, pp. 153-154) are used in this paper. The quantity $I(S)$, which is the total inhibition produced by cross-inhibitory fibers at any synapse, is proportional to the total *net* excitation

$$E(S) = \int \sigma(s, h)\, dh ,$$

at all the synapses, so that $E(s) = \frac{1}{\lambda} I(S)$, where λ has the same meaning as before (Rashevsky, 1940). The function $E(S)$ determines the total intensity E of the whole discriminatory center as a function of the intensity S of the peripheral stimulus. Using again the same notations as Householder (1939), we have the following expression for the function $E(S)$:

$$E(S) = \frac{\int_{h_1}^{h_2} (S, h)\, dh}{1 + \lambda (h_2 - h_1)} . \tag{1}$$

If, with Householder (1939), we consider the simple case

$$(S, h) = h(S - h), \tag{2}$$

and define a quantity x by (Householder, 1939):

$$Sx = S - 2h_1 = 2h_2 - S , \tag{3}$$

we have (Householder, 1939; Rashevsky, 1940):

$$\int_{h_1}^{h_2}(S\,,h)\,dh=\frac{S^3x\,(3-x^2)}{12}\,, \qquad (4)$$

and

$$h_2-h_1=Sx\,. \qquad (5)$$

Hence

$$E\,(S)=\frac{S^3x\,(3-x^2)}{12\,(1+\lambda\,S\,x)}\,. \qquad (6)$$

The quantity x satisfies the equation:

$$ux^3+x^2-1=0\,;\quad u=\frac{2\,\lambda}{3}\,S\,. \qquad (7)$$

Equations (6) and (7) give

$$E\,(u)=\frac{1}{\lambda^3}\,\frac{Su^3\,x\,(3-x^2)}{32\,(1+\frac{3}{2}\,ux)}\,. \qquad (8)$$

For large values of u, when $u >> 1$, $I\,(u)$ varies as u^2, since for such values of u, x is practically constant, decreasing slowly with u. This can be seen if we plot x as a function of u, obtained by solving equation (7) graphically, for different values of u. Hence, defining a as the average value of $(3-x^2)/12$ over the actually occurring range,

$$a=\frac{\overline{3-x^2}}{12\,\lambda}\,, \qquad (9)$$

and we have, introducing S instead of u into expression (8)

$$E\,(S)=aS^2\,. \qquad (10)$$

An actual graph shows that a relation of practically the same form as equation (10) holds also for small values of u, so that equation (10) may be used as a good approximation over a rather wide range of values of S.

Relation (10) may be applied to different problems in perception. In this paper we shall apply it to the problem of aesthetic judgments of geometrically similar patterns of different sizes.

Consider a series of similar polygons which are similarly oriented with respect to the observer, and which each consist of p equal sides (Rashevsky, 1938, 1940, 1942). As far as the excitation of L-centers is concerned, contemplation of each polygon results in a p-fold excitation of one L-center, the total excitation being p times the quantity $E(S)$. As for the intensity S of the corresponding peripheral stimulus, we assume it to be proportional to the length l of the side of the polygon (Householder, 1940) for not too large visual angles.

The total excitation of the L center will thus be proportional to l^2. Since in a series of similar and similarly oriented polygons, the excitation of the V, H, A, and possible symmetry centers remains the same, the total central excitation for each similar polygon should vary as

$$E_p = A + B\,l^2 . \tag{11}$$

It must, however, be remarked that the above relation cannot hold for extremely small values of l. For $l = 0$ the polygon shrinks to a point, and the excitations of the V, H, and A-centers vanish. What happens in this case neurobiophysically shall be discussed in another paper. For the present it is sufficient that relation (11) holds as long as we still perceive a polygon as such.

Besides the excitation of the V, H, A, and possible symmetry centers, the term A in relation (11) also contains the excitation due to the perception of the background on which the polygon is drawn. A presentation of a white card without any drawing on it results itself in a finite cortical excitation.

Since, according to previous publications, E is proportional to the intensity of pleasure (positive or negative) associated with the contemplation of a given pattern, equation (11) should represent the pleasantness values in a series of similar and similarly oriented polygons. By using some standard psychological method of scaling, it should be possible to verify relation (11) experimentally. Before proceeding to this, we should, however, consider a few other aspects of the situation.

All our considerations on the visual perception are limited to patterns of such a size which permits the detailed perception of the whole pattern without necessitating any movements of the head or even of the body as a whole. If a pattern is so large that it can be contemplated successfully only in parts by turning the head in different directions, the movement of the head sets up an additional pattern of proprioceptive stimulus, and those must be added to the regular visual or oculomotor stimuli in evaluating the pleasantness or unpleasantness of the contemplated pattern.

By restricting ourselves to sufficiently small patterns, we shall have a limiting factor, namely the size of the card, or more generally of the uniform background upon which the pattern is presented. When the over-all size of the pattern is equal or almost equal to the size of the background so that some elements of the pattern are very close to the "edge" of the background, the perception of that edge brings in additional elements which inhibit the centers involved in the perception of the pattern proper. In scanning the pattern, the eye may "jump" off into scanning the edge of the background. If the background is a card, as is actually the case in most experiments, then the surrounding back of the card adds also to the inhibiting effect. Thus the aesthetic value of the pattern as such will decrease due to the effect of the "edge" of the background. The law of the decrease must be determined by an extension of the theory somewhat along the lines suggested in Section 5 of a previous paper (Rashevsky, 1942). The theory in its present form does not yet predict the quantitative aspects of this decrease. Qualitatively, however, the theory does require such a decrease.

Hence we should expect the following situation to hold: for geometrically similar and similarly oriented polygons drawn on cards of the same size, the aesthetic value of the polygon should increase parabolically with the size of the polygons, when the polygons are sufficiently smaller than the cards. As the size of the polygons approaches the size of the card, the aesthetic value should begin to decrease.

If we have two series of similar and similarly oriented polygons identical in all respects except that one series is printed on larger cards than the other, then the deviation from the parabolic law in the series printed on smaller cards should occur at smaller sizes of the polygons.

Finally, the following considerations must be made. Even a blank card represents a visual stimulus which produces some central excitation and exerts an inhibitory effect on the centers involved in the perception of the pattern proper. Let S_p and S_c be the corresponding stimulus intensities for the patterns and the card. The quantity S_c in general may be expected to be an increasing function of the size of the card. Hence the value of E_p as given by equation (11) may be expected to slightly increase as the size of the card decreases. The amount of that increase will depend on the parameters of the cross inhibitory fibers. Thus with decreasing size of the card, we should expect an increase in the coefficent B in equation (11). As regards A , a more elaborate theory is needed to predict what would happen to it since, as remarked above, it contains itself the excitation due to the presentation of the blank card.

To verify all the above conclusions, the three polygons, represented on Figure 1, were used. Each polygon was printed in a series of six different sizes such that the length of each side were 3 mm; 0·45 mm; 0·6 mm; 0·75 mm; 0·9 mm and 1·2 mm. Five such se-

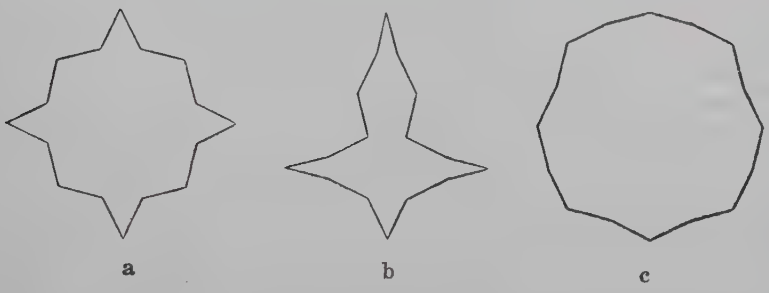

FIGURE 1

ries were made for each polygon. In one series each polygon was printed on a card having the size 12·5 × 17·5 cm; the second series of polygons was printed on cards 10 × 14 cm large; the third, on cards 8·33 × 11·7 cm, the fourth, on cards 7·8 × 10·9 cm, and the fifth, on cards 6·25 × 8·75 cm. Thus all cards are geometrically similar rectangles. Altogether there were 90 cards.

A simpler shape of the card, namely a square, would have been preferable. Inasmuch, however, as this experiment was a by-product of another experiment made for a different purpose, in which different other patterns were made on rectangular oblong cards, the above specified shapes of cards were used. The cards with the polygons were presented to 50 subjects. Each subject was asked to arrange the cards into 11 groups in order of their aesthetic preference. Using this procedure, it is possible to compute the psychophysical aesthetic ratings of each card with a polygon from the method of paired comparisons. The computations, however, are extremely elaborate and time-consuming when as many as 90 stimuli are used. Therefore, as a sufficiently good approximation the average group number of a given design was computed and used as a measure of the average aesthetic value. Figure 2 represents the results for polygons 1b. The other polygons gave similar results.

First of all, we see that on the largest card the aesthetic rating increases parabolically with the size l of the side of the polygon almost up to the largest size. A decrease is noticeable only for the very largest polygon. As the size of the card decreases, the parabolic relation breaks down at smaller sizes of the polygons, as is predicted by the theory. Finally, there is a slight increase of the steepness of the parabola with decreasing size of the card, although this effect is not too pronounced. It is more pronounced for polygons 1b. Thus the one quantitative and two qualitative predictions of the theory are verified. The constant A in equation (11) increases slightly with decreasing size of the card.

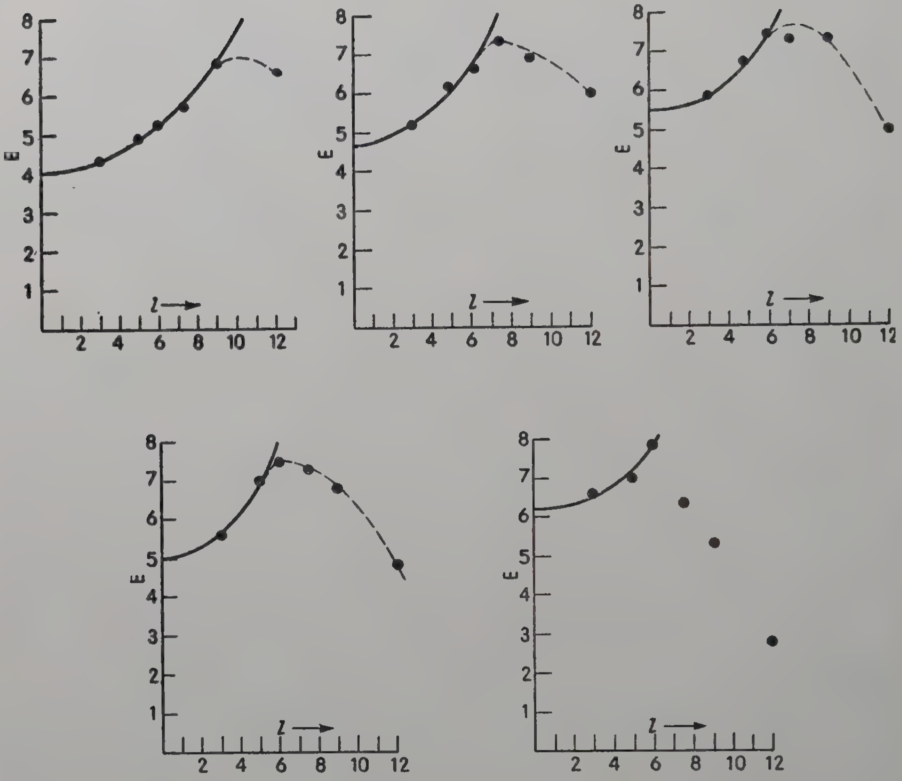

FIGURE 2

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LITERATURE

Guilford, J. P. 1936. *Psychometric Methods.* New York: McGraw-Hill Book Co.

Householder, A. S. 1939. "A Neural Mechanism for Discrimination." *Psychometrika,* **4**, 45-58.

Householder, A. S. 1940. "A Neural Mechanism for Discrimination: III. Visual Lengths." *Bull. Math. Biophysics,* **2**, 157-167.

Rashevsky, N. 1938. *Mathematical Biophysics. Physicomathematical Foundations of Biology.* Chicago: The University of Chicago Press.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology.* Chicago: The University of Chicago Press.

Rashevsky, N. 1942. "Some Problems in Mathematical Biophysics of Visual Perception and Aesthetics." *Bull. Math. Biophysics,* **4**, 177-191.

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ON THE THEORY OF BLOOD-TISSUE EXCHANGES:
I. FUNDAMENTAL EQUATIONS

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A mathematical analysis of the absorption of an inert gas by a heterogeneous system of n phases, e.g., a limb consisting of n tissues, is presented. The total uptake of gas, $\phi(t)$, up to time t is given in terms of arterial concentration, cardiac delivery, blood volume, and the volume, permeability, and partition coefficient of each tissue. The theory predicts how the uptake curve should change in shape under a variety of physiological conditions, and how from the numerical values of the constants the values of certain tissue constants, e.g. permeabilities, may be obtained.

Introduction. Many problems in the physiology of intact animals involve the absorption by the tissues of some substance which has entered the blood elsewhere. While experimental work along such lines can be and has been done with great care, the resulting data are not of the type that can be readily interpreted. Consequently, a need has arisen for a theoretical treatment of this subject. The present note is intended to submit such a consideration.

We will attempt here to treat the absorption of an inert gas in the blood by the tissues of a limb, and will use a vocabulary specific to this case. However, the mathematical results obtained are independent of vocabulary, and obviously could apply to anatomically different but functionally similar situations.

For the purpose of the analysis, we regard the limb to be constituted as follows: There exists a blood chamber of volume V_0 cm^3 (the blood volume). Into this chamber there is an inflow of blood at the rate of R cm^3 sec^{-1}; because blood and tissue fluid are practically incompressible, there is a liquid (blood + lymph) outflow also equal to R. The entering blood contains the gas in question at concentration C gm cm^{-3}. The (spatially) average concentration of gas in the blood chamber is x_0 gm cm^{-3}. In physiological contact with the blood chamber are n distinct tissues. The average concentration of gas in the i-th tissue is x_i gm cm^{-3}.

[*] The material in this article should be construed only as the personal opinion of the writers and not as representing the opinion of the Navy Department officially.

The matter of penetration constants of the tissues deserves some attention here, even though the general aspects are thoroughly treated by Rashevsky (1938) to whose work the reader is referred. When the intracellular "solvent" is the same as the extracellular "solvent", then we write by Fick's Law,

$$\begin{array}{l}\text{Penetration Rate} \\ \;\text{(gm cm}^{-2}\text{ sec}^{-1}\text{)}\end{array} \quad K\frac{S_i\,p'_i}{\delta}\,(x_0 - x_i) \equiv h_i\,S_i\,(x_0 - x_i)\,, \tag{1}$$

where K is a constant of proportionality, S_i is the absorbing surface area in cm^2, δ is the thickness of the cell membrane, and p'_i is the partition coefficient of the gas between water and "membrane substance". The constants, Kp'_i/δ are lumped together into a single h_i cm sec^{-1}, which is then the *permeability* of the membrane. On the other hand, when the "solvents" of the two sides are different, then for the penetration rate we obtain:

$$\text{Penetration Rate} = \frac{K\,S_i\,p'_i}{\delta}\left(x_0 - \frac{p''_i}{p'_i}\,x_i\right) \equiv h_i\,S_i\,(x_0 - \alpha_i\,x_i)\,, \tag{2}$$

where α_i is the partition coefficient of the gas between the external medium and the intracellular solvent. For some of the tissues, e.g. adipose, which we will consider, it is necessary to use equation (2) rather than equation (1). It is perhaps superfluous to point out that in the first case, the steady state will be attained for $x_0 = x_i$, while in our case it is attained when $x_0 = \alpha_i x_i$, and generally speaking, the steady state concentration within the tissue will be different from the steady state concentration in the blood.

Derivation. The setting up of our differential equations follows easily from the principle of material balance, which holds for the blood chamber and each tissue independently. Thus:

$$\frac{d(V_0\,x_0)}{dt} = R\,C - R\,x_0 - \sum_{i=1}^{i=n} h_i\,S_i\,(x_0 - \alpha_i\,x_i)$$

$$\frac{d(V_i\,x_i)}{dt} = h_i\,S_i\,(x_0 - \alpha_i\,x_i) \qquad i = 1, 2, \cdots n.$$

The substitution, $y_0 = C - x_0$ and $y_i = C_i/\alpha_i - x_i$ $(i = 1,\ 2,\ \cdots n)$ renders the equations homogeneous and somewhat simplifies the solution. We have then instead the set:

$$-V_0\frac{dy_0}{dt} = R\,y_0 + \sum_{i=1}^{i=n} h_i\,S_i\,(y_0 - \alpha_i\,y_i) \tag{3}$$

$$V_i \frac{dy_i}{dt} = h_i S_i (y_0 - \alpha_i y_i) \qquad (i = 1, 2, \cdots n). \tag{4}$$

We proceed to solve the set by the method of undetermined coefficients. The series:

$$y_i = \sum_{j=0}^{j=n} C_{ij} e^{-k_j t} \tag{5}$$

will be a solution of equations (3) and (4) provided we can find appropriate expressions for the C_{ij} and the k_j. This can be done as follows. The solutions (5) must, by hypothesis, satisfy equations (3) and (4) identically, which means that after substitution is made the coefficients of $e^{-k_j t}$ must vanish. Thus from putting relation (5) into relation (4) we obtain the solutions:

$$C_{ij} = \frac{h_i S_i}{\alpha_i h_i S_i - V_i k_j} C_{0j} \qquad (i = 1, 2, \cdots n). \tag{6}$$

On the other hand, we have yet to impose boundary conditions on equation (5). The two cases which concern the physiologist are absorption (when $t = 0$, $y_0 = C$, and $y_i = C/\alpha_i$) and desaturation, (when $t = 0$, $y_0 = 0$, and $y_i = 0$). Since our personal interest is in absorption, we will develop the equations for that case; however, it is clear that no mathematical difficulty is involved in the alternate conditions. For our case, then, when $t = 0$ relation (5) becomes:

$$\sum_{j=0}^{j=n} C_{0j} = C$$

and by (6),

$$\sum_{j=0}^{j=n} \frac{C_{0j}}{\alpha_i h_i S_i - V_i k_j} = \frac{C}{\alpha_i h_i S_i}, \qquad i = 1, 2, \cdots n. \tag{7}$$

Equation (7) is therefore a linear set of $(n+1)$ equations which can be solved for the C_{0j} by the usual methods. Then from equation (6) all the other C_{ij} are obtainable. Determinantal solution for C_{0j} gives:

$$\begin{aligned} C_{0j} = C (k_0 k_1 \cdots k_n)(V_1 V_2 \cdots V_n) \Delta_{ij} \Delta_{2j} \cdots \Delta_{nj} / k_j (\alpha_1 \alpha_2 \cdots \alpha_n) \\ \times (h_1 h_2 \cdots h_n)(S_1 S_2 \cdots S_n)(k_0 - k_j)(k_1 - k_j) \cdots \\ (k_n - k_j) \equiv A_{0j} C . \end{aligned} \tag{8}$$

where there is no factor, $k_j - k_j$, in the denominator, and where,

$$\Delta_{ij} = \alpha_i\, h_i \left(\frac{S_i}{V_i} \right) - k_j\,,$$

a function which we will have occasion to refer to later. Finally, putting equation (5) into equation (3), noting relations (6) and (8), we obtain the characteristic equation whose $(n+1)$ roots are the k_j:

$$V_0\, k_j + \sum_{i=1}^{i=n} \frac{\alpha_i\, h_i^2\, S_i^2}{\alpha_i\, h_i\, S_i - V_i\, k_j} - \left(R + \sum_{i=1}^{i=n} h_i\, S_i\right) = 0. \tag{9}$$

By the use of standard approximation methods, all the roots of equation (9) can be found once we have numerical values for V_0, R, α_i, h_i, V_i, and S_i. However, we may prove two useful facts about the roots of relation (9) without recourse to numerical methods.

I. *All the roots are positive.* This follows because if any one of them, say z, were negative, we could write the left hand member of equation (9) as:

$$F(z) = \left(\sum_{i=1}^{i=n} \frac{\alpha_i\, h_i^2\, S_i^2}{\alpha_i\, h_i\, S_i + V_i |z|} \right) - \left(V_0 |z| + R + \sum_{i=1}^{i=n} h_i\, S_i \right) .$$

The greatest value which the left-hand bracket could ever have would be, (for $|z| = 0$), $\sum h_i\, S_i$, whence the greatest value $F(z)$ could have would be $-(V_0|z| + R)$; thus $F(z)$ could never be 0, and therefore, contrary to our hypothesis k_j must always be positive.

II. *If the* $n+1$ *roots are, in descending order,* $\mathrm{r}^{(n)}, \mathrm{r}^{(n-1)}, \cdots \mathrm{r}^{(0)}$ *and if the products,* $\alpha_i\, \mathrm{h}_i \dfrac{\mathrm{S}_i}{\mathrm{V}_i}$ *are, in descending order,* $\mathrm{p}^{(n)}, \mathrm{p}^{(n-1)}, \cdots \mathrm{p}^{(1)}$, *then these quantities fall into the sequence,* $\mathrm{r}^{(n)} > \mathrm{p}^{(n)} > \mathrm{r}^{(n-1)} > \mathrm{p}^{(n-1)} \cdots \mathrm{r}^{(1)} > \mathrm{p}^{(1)} > \mathrm{r}^{(0)}$. For suppose that r'' and r' are roots such that $r'' > r'$. By hypothesis they both satisfy equation (9). On subtracting $F(r') = 0$ from $F(r'') = 0$, we obtain,

$$0 = V_0 + \sum_{i=1}^{i=n} \alpha_i\, h_i\, V_i \left(\frac{S_i}{V_i} \right)^2 \frac{1}{\left(\alpha_i\, h_i \dfrac{S_i}{V_i} - k'' \right) \left(\alpha_i\, h_i \dfrac{S_i}{V_i} - k' \right)}.$$

It must therefore be that some of the terms in the summation are negative, i.e., there is at least one tissue for which,

$$k'' > \alpha\, h \frac{S}{V} > k'.$$

Now imagine the roots k_j arranged in descending order, $r^{(n)} > r^{(n-1)} > \cdots > r^{(0)}$. By the reasoning just given, there must be a product, $\alpha\, h\, S/V$, between every two successive roots, but the number of such positions, n, is exactly equal to the number of tissues; thus if we adopt the notation, $p^{(n)} > p^{(n-1)} > \cdots > p^{(1)}$ for the descending sequence of products, we see that the two sequences must fall into the combined sequence, $r^{(n)} > p^{(n)} > \cdots > p^{(1)} > r^{(0)}$, and our theorem is proved.

From I and II it follows immediately that all the A_{0j} are positive, since all the k's are positive and since, by II, there are, for any k_j as many Δ_{ij}'s > 0 as there are $(k_i - k_j) > 0$, and as many Δ_{ij}'s < 0 as there are $(k_i - k_j) < 0$. However, the coefficients, C_{ij}/C, which we may call A_{ij}, need not be positive (see equation 6), nor must linear combinations of the A_{ij} necessarily be positive.

Next we turn to a consideration of the derivatives of k_j with respect to V_0, R, and the constants of the s-th tissue, α_s, h_s, V_s and S_s. These follow from equations (8) and (9). If by ω_j we denote the function:

$$\frac{1}{V_0 + \sum_{i=1}^{i=n} \alpha_i\, h_i\, V_i \left(\frac{S_i}{V_i} \right)^2 \Delta_{ij}^{-2}} > 0,$$

then we may write the various partial derivatives compactly as:

$$\frac{\partial k_j}{\partial R} = \omega_j > 0 \tag{10}$$

$$\frac{\partial\, k_j}{\partial (h_s\, S_s)} = \omega_j\, k_j^2\, \Delta_{sj}^{-2} > 0 \tag{11}$$

$$\frac{\partial k_j}{\partial\, \alpha_s} = \omega_j\, k_j\, V_s \left(\frac{S_s}{V_s} \right)^2 > 0 \tag{12}$$

$$\frac{\partial k_j}{\partial\, V_0} = -\, \omega_j\, k_j < 0 \tag{13}$$

$$\frac{\partial k_j}{\partial\, V_s} = -\, \omega_j\, k_j\, h_s^2 \left(\frac{S_s}{V_s} \right)^2 \Delta_{sj}^{-2} < 0\,. \tag{14}$$

The signs of these derivatives are evident enough. In connection with their numerical magnitudes it may be noted that all the derivatives are proportional to ω_j, a quantity which diminishes with increasing blood volume. The quantity, S/V, figures prominently in these functions, both by itself and where it appears in Δ_{ij}. Its presence stresses the physiological importance of the *shape* in which the tissue is disposed with respect to its blood supply.

The derivatives of the A_{ij} are complicated expressions whose signs and magnitudes cannot be ascertained from our work so far; consequently we have omitted them from this section.

We are now in a position to discuss the general solutions of the problem. Combining equations (5), (6), and (8) we obtain the concentrations of the gas in the blood and tissues as:

$$\begin{aligned} x_0 &= C\,\{1-(A_{00}\,e^{-k_0t}+A_{01}\,e^{-k_1t}+\cdots+A_{0n}\,e^{-k_nt})\} \\ x_1 &= C\left\{\frac{1}{\alpha_1}-(A_{10}\,e^{-k_0t}+A_{11}\,e^{-k_1t}+\cdots+A_{1n}\,e^{-k_nt})\right\} \\ &\cdots\cdots\cdots\cdots\cdots\cdots \\ x_n &= C\left\{\frac{1}{\alpha_n}-(A_{n0}\,e^{-k_0t}+A_{n1}\,e^{-k_1t}+\cdots+A_{nn}\,e^{-k_nt})\right\}. \end{aligned} \qquad (15)$$

Multiplying each concentration by the corresponding volume, we obtain the total *amount* of gas in the limb:

$$\begin{aligned} V_0\,x_0+V_1\,x_1+\cdots+V_n\,x_n = C\,\Bigg\{ & V_0+\frac{V_1}{\alpha_1}+\cdots+\frac{V_n}{\alpha_n} \\ & -(A_{00}\,V_0+A_{10}\,V_1+\cdots+A_{n0}\,V_n)\,e^{-k_0t} \\ & -(A_{01}\,V_0+A_{11}\,V_1+\cdots+A_{n1}\,V_n)\,e^{-k_1t} \\ & -(A_{0n}\,V_0+A_{1n}\,V_1+\cdots+A_{nn}\,V_n)\,e^{-k_nt}\Bigg\}. \end{aligned}$$

To expedite further discussion, we will adopt certain symbols for the quantities in this equation: We shall denote by

$$\phi = \text{total amount of gas in the limb} = \sum_{i=0}^{i=n} V_i\,x_i$$

$$\theta = \text{effective volume of the limb} = V_0+\sum_{i=1}^{i=n}\frac{V_i}{\alpha_i}$$

$$Q_j = \text{the coefficient of the } j\text{-th exponential} = \sum_{i=0}^{i=n} A_{ij}\,V_i$$

$$\psi = \text{the variable sum} = \sum_{j=0}^{j=n} Q_j\,e^{-k_jt}.$$

Our equation then becomes simply:

$$\phi = C(\theta-Q_0\,e^{-k_0t}-Q_1\,e^{-k_1t}-\cdots-Q_n\,e^{-k_nt}) = C(\theta-\psi). \qquad (16)$$

The solutions, $\phi(t)$, the total uptake, and $x_i(t)$ the uptake of the i-th tissue, are characterized by the following properties:

(1) They contain a number of exponential terms, $e^{-k_j t}$, equal to the number of tissues plus one.

(2) These exponential terms are all decaying terms, i.e., $k_j > 0$. The curves, $\phi(t)$ and $x_i(t)$ both approach asymptotes, $C\theta$ and C/α_i respectively.

(3) The coefficients of $e^{-k_j t}$, Q_j and A_{ij}, depend in general upon *all* the quantities, V_0, R, V_i, α_i, $h_i S_i$, and also on the shapes in which the tissue masses are disposed. Nothing is asserted about the signs of these coefficients.

(4) If the physical properties of the tissues are not radically different, then the mean value of the k's should be roughly equal to the mean value of $\alpha h S/V$ for the tissues. (The exact relationship is Theorem II.)

(5) The change in shape of $\phi(t)$ or $x_i(t)$ as V_0, R, V_i, α_i, or $h_i S_i$ is changed is governed mainly by the changes induced in the k_j's; therefor by equations (10) to (14), the curve approaches its asymptote *more rapidly* with increases in R, $h_i S_i$, or α_i, but it approaches it *more slowly* with increases in V_0 or V_i.

(6) Both ordinates $\phi(t)$ and $x_i(t)$ are proportional to the delivery concentration, C.

This concludes the purely mathematical considerations. The application to experimental data is considered elsewhere (Smith and Morales, 1944).

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LITERATURE

Rashevsky, N. 1938. *Mathematical Biophysics.* University of Chicago Press, Chicago.

Smith, R. E., and Morales, M. F. 1944. (In press.) "On the Theory of Blood-Tissue Exchanges: II. Applications." *Bull. Math. Biophysics,* 6, 133.

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